UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader
January 15, 1998

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

DATE: October 19, 1998

MEMORANDUM

SUBJECT: CHLORETHOXYFOS - *RE-EVALUATION OF Toxicology Endpoint Selection* -

FROM: Jess Rowland
Executive Secretary
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Steve Knizner
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Health Effects Division (7509C)

PC Code: 129006

SUMMARY: In the preliminary risk assessment done in August 1997, an oral NOEL was used for dermal occupational dermal exposure risk assessments. Since then the Agency has received, reviewed and accepted a 21-day dermal toxicity study in rats. The NOEL of 25 mg/kg/day in this study is based on inhibition of erythrocyte cholinesterase activity. This NOEL was selected for short and intermediate-term dermal occupational exposure risk assessments because: 1) the study tested the formulation product (granular) of concern for exposure; 2) the study was conducted in the sex (females) that was shown to be more sensitive to the effects of chlroethoxyfos; 3) the most sensitive endpoint (cholinesterase inhibition) was demonstrated via the route of exposure of concern (dermal); 4) the endpoint (cholinesterase inhibition) was observed 7 and 21 days post-treatment which is appropriate for the exposure periods of concern (1-21 days); and 5) the study design (dermal exposure) simulates real-life exposure scenario.

I. BACKGROUND

On November 16, 1994, the Health Effects Division's Toxicology Endpoint Selection Committee (TESC) met and selected the doses and endpoints for dietary and non dietary exposure risk assessments. At that meeting, the TESC selected an oral NOEL 0.06 mg/kg/day based on plasma cholinesterase inhibition observed in both sexes of dogs in a 6-month ocular toxicity study. The Agency used this oral NOEL and a 50% dermal absorption rate (for route-to-route extrapolation) to conduct its preliminary risk assessments for occupational dermal exposure HED Risk Assessment for Chlorethoxyfos (Fortress®, From: S.Robbins, HED to D. Edwards,RD dated August 21, 1995).

II. REVIEW OF A 21-DAY DERMAL TOXICITY STUDY

The Registrant, recently, submitted a 21-day dermal toxicity study in which adult female Crl:CD rats received 15 repeated dermal administration of Fortress 5G (approximately 5% chlorethoyxfos) at doses of 0 (vehicle control, deionized water), 0 (granular control, Fortress granules that did not contain chlorethoyxfos) at 25, 75 or 300 mg/kg, 6 hours/day for 21 consecutive days. This study was conducted with female rats only because previous studies have shown females to be more sensitive to the effects of chlorethoxyfos than males. The test substance, small water insoluble granules, was spread as thinly as possible onto a gauze dressing that was pre-moistened with 1 mL of deionized water. Cholinesterase measurements were done pre exposure and on study days 7 and 21. At the high dose (300 mg/kg/day) there were statistically significantly decreases in plasm and red blood cell (RB) cholinesterase activity on days 7 and 21 and in brain cholinesterase activity on day 7. At the mid dose (75 mg/kg/day), plasma and RBC cholinesterase activity was inhibited, however, only the depression in RBC reached statistical significance on day 21. The NOEL was 25 mg/kg/day and the LOEL was 75 mg/kg/day based on erythrocyte cholinesterase inhibition.

III. SELECTION OF DOSE FOR OCCUPATIONAL DERMAL RISK ASSESSMENTS

The NOEL of 25 mg/kg/day in this study is based on inhibition of erythrocyte cholinesterase activity. This NOEL was selected for short and intermediate-term dermal occupational exposure risk assessments because: 1) the study tested the formulation product (granular) of concern for exposure; 2) the study was conducted in the sex (females) that was shown to be more sensitive to the effects of chlroethoxyfos; 3) the most sensitive endpoint (cholinesterase inhibition) was demonstrated via the route of exposure of concern (dermal); 4) the endpoint (cholinesterase inhibition) was observed 7 and 21 days post- treatment which is appropriate for the exposure periods of concern (1-21 days); and 5) the study design (dermal exposure) simulates real-life exposure scenario.

NOTE: THE DOSES AND ENDPOINTS SELECTED FOR ACUTE AND CHRONIC DIETARY AS WELL AS INHALATION EXPOSURE RISK ASSESSMENTS BY THE TOXICOLOGY ENDPOINT SELECTION COMMITTEE (TES Document 11/16/94) REMAINS UNCHANGED.

IV. TOXICOLOGY ENDPOINT SELECTION

The toxicology endpoints selected for dietary and non-dietary risk assessments are presented below.

Exposure Duration	Exposure Route	Dose	Endpoint	Comments
Acute	Dietary	Acute RfD= 0.0006 mg/kg	Plasma cholinesterase	NOEL=0.06 mg/kg/day of and an Uncertainty Factor of 100 applied. No FQPA Safety Factor.
Chronic	Dietary	Chronic RfD= 0.0006 mg/kg/day	Overall Cholinesterase inhibition (ChEI)	NOEL=0.061 mg/kg/day based on ChEI in the 90-day, 6-month and 1-year studies in dogs. An Uncertainty Factor of 100 applied. No FQPA Safety Factor.
Short-Term (1-7 Days)	Dermal	NOEL = 25	Erythrocyte ChEI	A MOE of 100 is adequate for occupational exposure risk assessments. **There are no residential uses.**
Intermediate-Term (7-90 days)	Dermal	NOEL = 25	Erythrocyte ChEI	A MOE of 100 is adequate for occupational exposure risk assessments. **There are no residential uses.**
Long-Term (several months to life-time)	Dermal	None	None	Based on the use pattern (1 application/year), there is no potential long-term dermal exposure. Therefore, this risk assessment is not required.
Short,-Intermediate	Inhalation	NOEL= 0.06 mg/kg/day	Plasma cholinesterase inhibition	Oral NOEL selected due to lack of an appropriate inhalation study and the oral LD_{50} and inhalation LC_{50} for the technical and the formulation product (Fortress 5G) are both in Toxicity Category I. On this basis, the Agency has no reason to believe that chlorethoxyfos is less potent in term of toxicity by the inhalation route. Since an oral NOEL was selected, the use of 100% (default) inhalation absorption rate is required for risk assessment. A MOE of 100 is adequate for occupational exposure risk assessments. There are no residential uses.
Long-Term (several months to life-time)	Inhalation	None	None	Based on the use pattern (1 application/year), there is no potential long-term dermal exposure. Therefore, this risk assessment is not required.